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(54) Title: CONTROLLED RELEASE SOLID DOSAGE FORMS OF LITHIUM CARBONATE

(57) Abstract

Invented is a process for preparing controlled release solid dosage forms of lithium carbonate and controlled release solid dosage forms of medicaments prepared thereby.

18

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CONTROLLED RELEASE SOLID DOSAGE FORMS OF LITHIUM
CARBONATE

Field of the Invention

5 This invention relates to processes for preparing controlled release solid dosage forms of lithium carbonate (Li_2CO_3) for oral administration and controlled release solid dosage forms of lithium carbonate.

Background of the Invention

10 Lithium carbonate is indicated in the treatment of manic episodes of manic-depressive illness and is commercially available in controlled release tablets under the tradename Eskalith CR®. In addition to the active ingredient - lithium carbonate, approx. 91%, - Eskalith CR® tablets contain alginic acid, 1%, gelatin, 4%, sodium starch glycolate, approx. 4%, iron oxide, trace amount, and magnesium stearate, 1%, as 15 inactive ingredients. Eskalith CR® tablets have been manufactured for a number of years by a high shear wet granulation process that is characterized by a significant time dependent retardation in the dissolution rate of lithium carbonate which results in a shortened shelf-life for the product. Furthermore, significant batch to batch variability in the release rates of the active ingredient, both initially and on storage, is a persistent 20 problem with the current process/product. The batch to batch variability in the release rate of lithium carbonate is of particular concern to the therapeutic use of this agent because lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels. Lithium toxicity is so much of a concern that it is recommended that facilities for prompt and accurate serum lithium determinations be 25 available before initiating therapy with lithium carbonate.

Thus, there is a need in the art for processes for preparing controlled release solid dosage forms of lithium carbonate and controlled release solid dosage forms of lithium carbonate which exhibit batch to batch consistency in release rates and stabilized dissolution profiles over time.

30 As disclosed herein, suitable controlled release solid dosage forms of lithium carbonate and processes for preparing the same have now been discovered

Detailed Description of the Invention

All publications, including but not limited to patents and patent applications, 35 cited in this specification are herein incorporated by reference as though fully set forth.

By the term "hydrophobic waxy material", "waxy material" or "wax" as used herein, is meant a fatty acid, alcohol or ester, alone or an admixture thereof. More

specifically, the fatty acid may have from about 10 to about 22 carbon atoms and may be, for example, decanoic, stearic, palmitic, lauric or myristic acid.

The fatty alcohols may have from about 14 to about 31 carbon atoms and may be, for example, lauryl alcohol, cetyl, stearyl, myristyl, carbucyl or ceryl alcohol.

5 The esters may be mono-, di-, or triglyceryl esters. The hydrophobic waxy material may be modified by waxy materials of natural or synthetic sources. Exemplary of such waxes are beeswax, spermaceti wax or carnauba wax.

Preferred hydrophobic waxy materials for use herein include: cetyl alcohol, carnauba wax, glyceryl behenate (Compritol® from Gattefosse Corp.) glyceryl 10 palmitostearate (Precirol® from Gattefosse Corp.) glyceryl monostearate and glyceryl distearate.

By the term "dissolution rate stabilizer" as used herein is meant organic acids such as fumaric acid, citric acid, tartaric acid, maleic acid, malic acid, ascorbic acid, succinic acid, sorbic acid and their anhydrides and salts. Poorly water soluble acids are 15 preferred. Particularly preferred acids for use herein are fumaric acid and malic acid.

By the term "formulated into solid dosage forms" and derivatives thereof, as used herein preferably includes filling hard gelatin capsules and compressing into tablets.

By the term "thermal infusion" and derivatives thereof, as used herein is meant 20 that the pharmaceutically active material - lithium carbonate - is blended with a hydrophobic waxy material and optional pharmaceutically acceptable excipient(s) and then optionally compacted, followed by dry granulation in a granulator at a suitable thermal infusion temperature and then optionally milled and screened to form thermal infusion granules.

25 When referring to thermally infusing blends in which the percentage of hydrophobic waxy material is about 30% by weight, preferably less than 20%, in relation to the pharmaceutically active material, the term "suitable thermal infusion temperature" or "thermal infusion temperature" and derivatives thereof, as used herein includes ambient temperature and temperatures above the extrapolated onset 30 temperature, preferably less than 15°C above the melting temperature, of the hydrophobic waxy material.

The "extrapolated onset temperature" represents that temperature corresponding to the intersection of the pre-transition baseline with the extrapolated leading edge of the endotherm (melting curve). For glyceryl behenate the extrapolated onset 35 temperature is about 68°C.

Additional aspects relating to thermal infusion are found in International Publication Number WO 94/27557, having an International Publication Date of

December 8, 1994, the entire specification of which is hereby incorporated by reference.

The present invention relates to a process for preparing controlled release solid dosage forms of lithium carbonate (Li_2CO_3) which comprises blending lithium carbonate, a hydrophobic waxy material, preferably glyceryl behenate, a dissolution rate stabilizer, preferably fumaric acid, and optional pharmaceutically acceptable excipient(s), preferably microcrystalline cellulose, in a suitable mixer. The blend is converted into granules of desired particle size distribution by a dry granulating process which preferably consist of the steps of roller compacting, milling and screening. The 10 granules thus prepared are formulated into solid dosage forms.

The order in which the indicated ingredients are utilized in the presently invented process is not critical. All orders of addition of the indicated ingredients are within the scope of the invention. However, the most advantageous process comprises blending lithium carbonate, in about 40 to 90% by weight preferably 65 to 85% most 15 preferably 80 to 85%, a hydrophobic waxy material, preferably glyceryl behenate, in about 5 to 30% by weight preferably 5 to 25%, most preferably 8-23% in relation to the pharmaceutically active material, and optional, pharmaceutically acceptable excipient(s), preferably microcrystalline cellulose, in about 5 to 10% by weight, in a suitable mixer. The blend is converted into granules of desired particle size distribution 20 by a dry granulating process which preferably consist of the steps of roller compacting, milling and screening. The granules thus prepared are blended with a dissolution rate stabilizer, preferably fumaric acid, in an amount greater than 1% to about 15% by weight, preferably 3 to 15 %, most preferably about 6 to 13%, and a pharmaceutically acceptable excipient, preferably microcrystalline cellulose, in about 5 to 30% by 25 weight, preferably 10 to 25%, most preferably 10 to 20%, in a suitable mixer and formulated into solid dosage forms.

In noting the percentages of the ingredients above and throughout the specification and the claims, the wax content as well as the other excipients are always stated in relation to the active material (for example, 85/15 means 85 parts of lithium 30 carbonate blended with 15 parts of an excipient such as glyceryl behenate or 80/15/5 means 80 parts of lithium carbonate, 15 parts of an excipient such as glyceryl behenate and 5 parts of an excipient such as microcrystalline cellulose).

An alternative step in the presently invented process involves subjection of a blend, prepared as described herein, to thermal infusion prior to or during the dry 35 granulating process.

The ability of the presently invented process to prepare the presently invented controlled release solid dosage forms of lithium carbonate, which exhibit batch to batch

consistency in release rates and stabilized dissolution profiles over time, is primarily attributed to the addition of a dissolution rate stabilizer to the formulation and using a dry granulating process instead of a wet granulating process as was previously used.

Additional pharmaceutically acceptable excipients which are contemplated for 5 use in the process and compositions of the present invention include release rate modulating polymers, such as high molecular weight poly(ethylene oxide) (available under the name Polyox WSR of Union Carbide Corporation), lactose, polyvinylpyrrolidone and pharmaceutically acceptable coloring agents.

In a general procedure for the processes of the current invention, lithium 10 carbonate, a hydrophobic waxy material and optional pharmaceutical excipients are blended in a suitable mixer and granules of desired particle size distributions are manufactured in a dry granulating process, preferably by slugging or compacting, milling and screening. The granules may be produced using a continuous process or a batch process. Granules of desired mesh size (such as #18 & #80 mesh, i.e., passing 15 through #18 mesh sieve but retained on #80 mesh sieve) are prepared, optionally by subjecting a blend, prepared as described herein, to thermal infusion prior to or during the dry granulating process.

The granules thus prepared are blended with optional pharmaceutical excipients and a dissolution rate stabilizer, preferably an organic acid such as fumaric acid, and 20 filled into hard gelatin capsules or compressed into tablets. In another variation of the process, the powdered blend is granulated by melt granulation instead of by roller compaction. This melt granulation is milled to produce granules with a desired particle size distribution. These granules are blended with optional pharmaceutical excipients and a dissolution rate stabilizer, preferably an organic acid, and filled into hard gelatin 25 capsules or compressed into tablets.

By the term "pharmaceutically acceptable excipients" as used herein is meant additives such as diluents, fillers, and binders which are optionally utilized in accordance with the process of the present invention. The excipients commonly used in pharmaceutical industry are well described in literature such as described in Handbook of Pharmaceutical Excipients, A. Wade and P. J. Weller (Editors), American 30 Pharmaceutical Association (1994). Pharmaceutically acceptable fillers and diluents include but are not limited to lactose (hydrated as well as anhydrous), starch [unmodified (corn starch) or modified (for e.g., Starch 1500 available from Colorcon)], mannitol, sorbitol, cellulose, inorganic sulfates and phosphates. Pharmaceutically acceptable binders include but are not limited to gelatin, corn starch, modified starch 35 (Starch 1551, pregelatinized starch), hydroxypropyl methyl cellulose (HPMC) and hydroxypropyl cellulose(HPC). Examples of excipients suitable for modified release

applications in accordance with the present invention include but are not limited to) waxy materials such as glyceryl behenate (Compritol®), glyceryl palmitostearate (Precirol®), saturated polyglycolized glycerides (Gelucire®) [all from Gattefosse s.a., France], carnauba wax and a series of high molecular weight non-ionic water-soluble 5 high molecular weight poly(ethylene oxide) polymers (Polyox® WSR, Union Carbide Corp.).

The present invention also relates to novel compositions of lithium carbonate prepared by the dry granulating process described above. The presently invented compositions of lithium carbonate comprise lithium carbonate, a hydrophobic waxy 10 material, preferably glyceryl behenate, a dissolution rate stabilizer, preferably fumaric acid, and optional pharmaceutically acceptable excipient(s), preferably microcrystalline cellulose.

The presently invented compositions of lithium carbonate suitably comprise lithium carbonate, in about 40 to 90% by weight preferably 65 to 85% most preferably 15 80 to 85%, a hydrophobic waxy material, preferably glyceryl behenate, in about 5 to 30% by weight preferably 5 to 25%, most preferably 8-23% in relation to the pharmaceutically active material, pharmaceutically acceptable excipient(s), preferably microcrystalline cellulose (added extragranularly or both intra- and extra-granularly), in about 5 to 30% by weight, preferably 10 to 25%, most preferably 15 to 25%, and a 20 dissolution rate stabilizer, preferably fumaric acid in an amount greater than 1% to about 15% by weight, preferably 3 to 15%, most preferably 6 to 13%.

A further contemplated aspect of the presently invented process and compositions relates to subsequently coating the prepared compositions with a moisture barrier or controlled release polymer coating.

25 Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

30 **Examples of Formulations**

Example 1

Lithium carbonate USP by itself (batchsize: 2 kgs) was roller compacted at 750-800 PSI using a Fitzpatrick roller compactor, milled using a Fitzmill using a perforated screen and sifted to produce #18-40 mesh granules [the sieve fraction passing through # 18 35 mesh screen but collected on the #80 mesh screen]. 450 mg lithium carbonate tablets weighing 584 mg (77% granules blended with 22.5% microcrystalline cellulose and

0.5% magnesium stearate) were manufactured from these granules using a Stokes tablet press. (Formula A Tablets).

Example 2

A blend containing 87.3% lithium carbonate, 0.2% iron oxide, 7.5% glyceryl behenate and 5.0% microcrystalline cellulose [batchsize: 50 kgs] was roller compacted using a Fitzpatrick L-83 chilsonator, milled and sifted. 15 kgs of #18-40 mesh granules were heat treated in a fluid bed granulator [Glatt GPCG-UD30H] at $64 \pm 2.0^{\circ}\text{C}$ for 15 min. 12.0 kgs of the heat treated granules were blended with 2.925 kgs of microcrystalline cellulose and 0.075 kg magnesium stearate using a bin blender and compressed into 450 mg lithium carbonate tablets [tablet weight: 644 mg (Formula B Tablets)] using a Hata tablet press.

Example 3

95 kgs lithium carbonate and 5 kgs Compritol were blended in a 10 cu.ft. V-blender. #18-40 mesh size dry granules were manufactured using a continuous cycle Fitzpatrick 4L x 10D chilsonator system. In this continuous cycle system, the material is roller compacted, milled and sifted into three fractions - oversize ($>\#18$ mesh) granules, #18-40 mesh granules and fines ($<\#40$ mesh); the oversize granules and fines are blended with virgin material, and the process continues. 7.4 kgs of #18-40 mesh granules were blended with 2.55 kg microcrystalline cellulose and 0.05 kg magnesium stearate and compressed into 450 mg tablets (tablet weight: 640.1 mg [Formula C Tablets]). 7.4 kgs of #18-40 mesh granules were blended with 2.05 kg of microcrystalline cellulose, 0.5 kg tartaric acid and 0.05 kg magnesium stearate and compressed into 450 mg lithium carbonate tablets [tablet weight: 640.1 mg (Formula D Tablets)]. 7.4 kgs of #18-40 mesh granules were blended with 2.05 kgs of microcrystalline cellulose, 0.5 kg fumaric acid and 0.05 kg magnesium stearate and compressed into 450 mg tablets [tablet weight: 644.1 mg (Formula E Tablets)]. 7.4 kgs of #18-40 mesh granules were blended with 2.175 kgs of microcrystalline cellulose, 0.375 kg fumaric acid and 0.05 kg magnesium stearate and compressed into 450 mg tablets [tablet weight: 644.1 mg (Formula F Tablets)].

Example 4

A blend [batchsize: 67.0 kgs] containing 79.8% lithium carbonate, 0.2% iron oxide pigment (Cosmetic Ochre) and 20% Compritol is roller compacted, milled and sifted. 53.07 kgs of #18-40 mesh granules were blended with 9.63 kgs of microcrystalline cellulose, 4.0 gks of fumaric acid and 300.0 gm magnesium stearate and compressed into 450 mg tablets [tablet weight: 670 mg (Formula G Tablets)].

Example 5

- A blend [batchsize: 20 kgs] containing 84.8% lithium carbonate, 0.2% an iron oxide pigment and 15% Compritol was roller compacted, milled and sifted. 1061.4 gms of #30-80 granules were blended with 192.6 gm microcrystalline cellulose, 80.0 gm fumaric acid and 6.0 gm magnesium stearate and compressed into 450 mg tablets [tablet weight: 670.0 mg (Formula H Tablets)]. A mixture of 849.0 gm #30-80 granules and 212.2 gm #80-140 mesh granules [i.e., 80% of #30-80 and 20% of #80-140 mesh granules] was used in place of the #30-80 mesh granules in Formula H Tablets above to produce 450 mg tablets [batchsize: 1340 gms; (Formula I Tablets)]. 1061.4 gm granules passing through a #30 mesh screen were used in place of the #30-80 mesh granules in Formula H Tablets above to produce 450 mg tablets [batchsize: 1340 gms; (Formula J Tablets)].

Example 6

- 15 A blend [batchsize: 30 kgs] containing 82.3% lithium carbonate, 0.2% an iron oxide pigment, 12.5% Compritol and 5.0% microcrystalline cellulose was roller compacted, milled and sifted. 16824.6 gms of #30-140 granules were blended with 1852.4 gm microcrystalline cellulose, 1230.8 gm fumaric acid and 92.4 gm magnesium stearate and compressed into 450 mg tablets [tablet weight: 650.0 mg (Formula K Tablets)].

20

Dissolution Testing

- The 450 mg lithium carbonate tablets of Examples 1 to 3 were initially tested in purified water at 37°C using USP Apparatus 1 (Basket @ 100 rpm). The percentage release in relation to the USP reference material was determined as a function of time 25 using an atomic absorption spectrophotometer or an inductively coupled plasma emission spectrometer. The tablets of Examples 4 and 5 were tested in 0.1N HCl containing 0.05% SDS using USP Apparatus 1 (Baskets@ 100 rpm) while the tablets of Example 6 were tested in 0.1N HCl containing 0.05% SDS using USP Apparatus 1 (Baskets@ 50 rpm).

Dissolution Profiles from Tablets on Stability**Table 1 : Dissolution Data for Lithium Carbonate Prototype Formulas**

Condition	<u>% Release</u>		
	1 Hour	3 Hours	7 Hours
Foumula A			
Initial	84	99	
40°C/75% RH, 1 mo	33	77	96
Formula B			
Initial	27	47	63
Ambient, 7 mo	18	38	59
30°C, 1 mo	26	47	64
30°C/75%RH, 1 mo	26	45	62
30°C/75%RH, 3 mo	15	31	46
30°C/75% RH, 6 mo	13	29	44
40°C, 1 mo	21	40	56
40°C/75% RH, 1 mo	16	32	47

5

The data represented in Table 1 shows that tablets of Formula A released the drug rapidly while tablets of Formula B released steadily for over 7 hours. However, the storage of tablets both formulas in sealed high density ploy(ethylene) bottles at accelerated temperatures, such as 40°C/75%RH, resulted in a significant retardation in 10 dissolution. Formula B tablets stored at 30°C/75% RH for 6 months also showed significant drops in release rates.

Table 2 : Dissolution Profiles of Lithium Carbonate Formulations on Stability

Formula	Condition	% Release			
		1 hr	3 hr	7 hr	12 hr
Formula C	No Acid				
	Initial	37	62	82	92
Formula D	5.0 % Tartaric Acid				
	Initial	40	67	89	98
Formula E	5.0 % Fumaric Acid				
	Initial	33	57	76	87
Formula F	3.75 % Fumaric Acid				
	Initial	37	66	89	98

The data represented in Table 2 presents drug release profiles from controlled
5 release tablets of lithium carbonate prepared as described in Example 3. The data in
this table indicates that incorporating an organic acid in a tablet formulation of lithium
carbonate, such as tartaric acid or fumaric acid of the present invention, stabilizes the
dissolution profile over time [by retarding the slowing down in dissolution]. The
duration of stabilization has been shown to depend on the temperature of storage, the
10 lower the temperature of storage, the longer the duration of dissolution stabilization that

could be achieved. Also, highly water soluble acids such as citric and tartaric acids, appear to provide stabilization for shorter durations than the poorly water soluble fumaric acid [solubility of citric or tartaric acid in water is about a gram per ml. while that of fumaric acid is 6 mg per ml.]. The dissolution data on multiple batches of
 5 Formula E suggested that batch to batch consistency in release rates.

Table 3 : Dissolution Data for Lithium Carbonate Controlled Release Formulas

	<u>% Release</u>		
	1 hr	3 hr	7 hr
Formula G			
Initial	22	51	84
30°C/60% RH, 3 mo	21	54	90
40°C/75% RH, 3 mo	16	40	75
Formula H			
Initial	26	56	86
30°C/60% RH, 3 mo	25	53	84
40°C/75%RH, 3 mo	21	52	81
Formula I			
Initial	22	51	88
30°C/60% RH, 1 mo	21	52	82
40°C/75% RH, 1 mo	19	45	83
30°C/60%RH, 6 mo	20	50	91
Formula J			
Initial	23	58	94
25°C/60% RH, 6 mo	21	49	89
25°C/60%RH, 12 mo	20	46	81
30°C/60% RH, 3o	18	45	86
30°C/60%RH, 6 mo	20	45	83
30°C/60% RH, 12 mo	20	47	87
40°C/75% RH, 1 mo	17	44	87
40°C/75% RH, 6 mo	19	46	93
Formula K			
Initial	22	52	85

The data represented in Table 3 presents drug release profiles from controlled release tablets of lithium carbonate prepared as described in Examples 4 and 5. The data in this table indicates that incorporating fumaric acid in a tablet formulation of lithium carbonate, effectively stabilizes in-vitro release profiles from the tablets over time and provides for batch to batch consistency in release rates.

The above Examples demonstrate the ability of the presently invented process to prepare controlled release solid dosage forms of lithium carbonate and the ability of the presently invented controlled release solid dosage forms of lithium carbonate to exhibit batch to batch consistency in release rates and stabilized dissolution profiles over time.

While the preferred embodiments of the invention are illustrated by the above, it is to be understood that the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming within the scope of the following claims is reserved.

What is claimed is:

1. A process for preparing controlled release solid dosage forms of lithium carbonate which comprises the steps of:
 - 5 (a) blending lithium carbonate, a hydrophobic waxy material, a dissolution rate stabilizer and optional pharmaceutical excipients; and
 - (b) formulating the resulting blend into solid dosage forms.
2. The process of claim 1 which comprises the steps of:
 - 10 (a) blending lithium carbonate, a hydrophobic waxy material, a dissolution rate stabilizer and optional pharmaceutical excipients;
 - (b) dry granulating the resulting blend into granules; and
 - (c) formulating the resulting granules into solid dosage forms.
- 15 3. The process of claim 2 which comprises the steps of:
 - (a) blending lithium carbonate, a hydrophobic waxy material and optional pharmaceutical excipients;
 - (b) dry granulating the resulting blend into granules;
 - (c) blending the resulting granules with optional pharmaceutical excipients and
 - 20 a dissolution rate stabilizer, and
 - (c) formulating the resulting blend into solid dosage forms.
4. The process of claim 3 which comprises the steps of:
 - 25 (a) blending lithium carbonate a hydrophobic waxy material and optional pharmaceutically acceptable excipients;
 - (b) roller compacting, milling and sieving the resulting blend to produce granules of a desired particle size distribution;
 - (c) -- preparing a compression mix by blending said granules with optional pharmaceutically acceptable excipients and a dissolution rate stabilizer; and
 - 30 (d) filling said compression mix into hard gelatin capsules or compressing into tablets.
5. The process of claim 4 which comprises:
 - 35 (a) subjecting lithium carbonate granules prepared as in claim 4, step (a) to thermal infusion;
 - (b) preparing a compression mix by blending said granules with optional pharmaceutically acceptable excipients and a dissolution rate stabilizer; and

(c) filling said compression mix into hard gelatin capsules or compressing into tablets.

6. The process according to any one of claims 1 to 5 wherein the
5 dissolution rate stabilizer is selected from tartaric acid, citric acid, fumaric acid, ascorbic acid, succinic acid, maleic acid, malic acid or sorbic acid or any pharmaceutically acceptable organic acid anhydride or salt thereof.

7. Controlled release solid dosage forms of lithium carbonate prepared
10 according to any one of claims 1 to 6.

8. A controlled release solid dosage form of lithium carbonate containing:
15 (a) about 40 to 90% by weight lithium carbonate;
(b) a hydrophobic waxy material in about 5 to 30% by weight;
(c) a dissolution rate stabilizer in an amount greater than 1% to about 15%
by weight; and
(d) optional pharmaceutically acceptable excipients.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US98/20579

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/22, 9/52

US CL :424/456, 457, 464, 465, 468

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/456, 457, 464, 465, 468

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

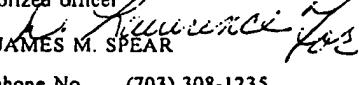
C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,415,878 A (NEWTON et al) 16 May 1995, see entire document.	1-6

 Further documents are listed in the continuation of Box C. See patent family annex.

•	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Z"	document member of the same patent family
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Date of the actual completion of the international search 21 DECEMBER 1998	Date of mailing of the international search report 26 JAN 1999
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Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized Officer JAMES M. SPEAR 
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/20579**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.: 7 because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.